UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/033,055	12/27/2001	Ronald M. Burch	200.1079CON	7860

23280 7590 01/19/2005

DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

EXAMINER	
CELSA, BENNETT M	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 01/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/033,055	BURCH ET AL.	
	Examiner	Art Unit	
	Bennett Celsa	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38,39 and 46-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38,39 and 46-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/29/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment dated 10/29/04 is acknowledged.

Status of the Claims

Claims 38-39 and 46-50 are currently pending and under consideration.

Claims 40-45 have been cancelled.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objection (s) and/or Rejection (s)

The rejection of claims 38-44 and 46-47 under 35 U.S.C. 103(a) as being unpatentable over Baker et al. 937 and Penning et al. applied to claims 38-44 and 46-47 above, and further in view of Mayer et al. US Pat. No. 5,834,479 (11/98) is hereby withdrawn in view of applicant's amendment (e.g. canceling claims 40-44).

Outstanding Objection (s) and/or Rejection (s)

Claim Rejections - 35 USC 103

1. Claims 38-39, 46-48 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al. US Pat. No. 4,569,937 (2/86) and Penning et al. J. Med. Chem. Vol. 40(9) (April 1997) pages 1347-1365.

Baker et al. teach pharmaceutical compositions for relieving pain in humans or mammals (e.g. mice, rats etc.) comprising a combination of :

a. a narcotic analgesic (preferably oxycodone: see formulations col. 4-8; mice data in col. 8-10; patent claims), or a pharmaceutically acceptable salt thereof; and

b. ibuprofen (a non-steroidal anti-inflammatory drug or NSAID: see col. 1-2), or a pharmaceutically acceptable suitable salt thereof,

in a weight ratio of about 1:800 (e.g. .001:1) to 1:1 (compare to present claim 47:See col. 2) with oxycodone amounts of about 5 mgs-600mgs (compare to present claim 46). The Baker reference teaches oral administration (e.g. see present claim 39), which can be coadministered in a single dosage form (e.g. see col. 3-8: and present claim 40) or sequentially administered (e.g. see i.e. col. 8-9; mice are dosed sequentially). The oral dosage forms include "sustained release" formulations (e.g. tablets, capsules, etc: see col. 3-4, especially col. 4) which include "sustained release carriers". The Baker et al. reference teach that dose ratios can be adjusted and that the analgesic activity of the combined oxycodone and ibuprofen activity is unexpectedly enhanced or synergistic i.e. the resulting activity is greater than the activity expected from the sum of the activities of the individual components, thereby permitting reduced dosages of narcotic analgesics (e.g. oxycodone) AND which diminishes adverse side effects (e.g. addiction) and toxicity which would result from the otherwise required amounts of the individual drug components resulting from high dosages of oxycodone or NSAIDs such as ibuprofen. See e.g. col. 1-2; col. 3, lines 19-32. Accordingly, Baker would teach the use of therapeutic and subtherapeutic amounts of oxycodone and/or ibuprofen in view of the additive or synergistic nature of the combinations and the desire to reduce the toxicity and/or side-effects of both agents; and as required by the doctor for his/her particular

patient., including dosage optimization e.g. dosage overlapping of active ingredients. See e.g. col. 3 where dosage is modified to suit the particular patient.

The Baker analgesic composition differs from that presently claimed in that it fails to teach the substitution of celecoxib for ibuprofen into the Baker compositions.

Penning et al. teach both *in vitro* and *in vivo* (up to phase 2 clinical trials) that the selective COX2 inhibitor celecoxib (SC-58635):

a. had potent anti-inflammatory activity equivalent to NSAID's without the gastric toxicity side-effect of the NSAID's (e.g. celecoxib had no acute GI toxicity in rats at doses of up to 200 mg/kg and no chronic GI toxicity at doses up to 600 mg/kg);

b. has good bioavailability, is well distributed, and has an excellent safety profile;

c. is at least as potent against pain as aspirin in a phase 1 human clinical dental pain study.

See Penning abstract; page 1347; pages 1352-1354; Tables1-10.

Accordingly, one of ordinary skill in the art would have been motivated to substitute celecoxib for ibuprofen in the Baker reference compositions in light of the Penning reference teaching that celecoxib is analgesically potent with less side effects (e.g. as compared to NSAIDS e.g ibuprofen) in both *in vitro* and *in vivo* models, including humans.

Additionally, it is noted that the instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two (or more) compositions each of which is taught by the prior art to be useful for the same purpose.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to modify the Baker reference analgesic composition by substituting celecoxib for ibuprofen in Bakers composition in light of the benefits of celecoxib (potent analgesia/decreased side effect as compared to NSAID e.g. ibuprofen) as taught by the Penning reference.

New Objection (s) and/or Rejection (s)

2. Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al. '937 and Penning et al. as applied to claims 38-39, 46-48 and 50 above, and further in view of Oshlack et al. US Pat. No. 5,472,712 (12/95) or Oshlack et al. US Pat. No. 6,294,195 (9/01: effectively filed 10/93 or earlier).

The substance of the above obviousness rejection is hereby incorporated by reference in its entirety.

Although the Baker reference teaches oral dosage forms which include "sustained release" formulations (e.g. tablets, capsules, etc: see col. 3-4, especially col. 4) utilizing "sustained release carriers", the Baker reference fails to explicitly teach "a sustained release carrier which provides a sustained release of the oxcodone and/or ... salt thereof".

However, the use of sustained release dosage forms for opioid analgesics, including oxycodone which utilize sustained release carriers employing beads which are coated with the opioid drug or which include substrate layers which include the drugs is

known in the art to effectuate delayed release of extended duration. E.g. see Oslack et al. and Oshlack patent references.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to utilize sustained release carriers for oxycodone including beads/layers as taught by the Oshlack and Oshlack et al. patents for use in the Baker compositions since Baker specifically teaches using "sustained release formulations" and further in view of the advantages of utilizing the Oshlack patent sustained release carriers including delayed drug release of extended duration.

Discussion

Applicant's arguments directed to the above obviousness rejections were considered but deemed nonpersuasive for the following reasons.

Initially, it is noted in response to applicant's argument, the above rejections were modified to remove a"consisting essentionally of" embodiment that included three analgesics (e.g. celebrex, oxycodone and ibuprofen). It is further noted that the above rejection was further modified in response to applicant's amendment (e.g. canceling claims and adding new claims addressing delayed release).

Applicant argues:

1. "... that the purported invention of Baker et al. is directed to pharmaceutical compositions of narcotic analgesics and ibuprofen which '... exhibit unexpectedly enhanced analgesic activity ..." (emphasis provided by applicant); AND

2. that "Baker et al. is limited to combinations wherein the NSAID is ibuprofen and does not teach or suggest that the purported "unexpectedly enhanced analgesic activity would occur with an NSAID which is different than ibuprofen."

3. Therefore "substituting ibuprofen with celexocib would result in a dosage form which is not directed to the principle of operation described in Baker et al. (i.e. the purported synergism of narcotic analgesics and ibuprofen); and

4. Changing "the principle of operation of the prior art invention" is indicia of nonobviousness citing MPEP 8th edition, Revision 2, p. 2100-132.

This argument was considered, but deemed nonpersuasive for the following reasons.

Initially, it is noted that three (3) basic criteria must be met in order to establish a *prima facie* case of obviousness:

1. There must be some suggestion or motivation, either in the reference themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings;

2. There must be a reasonable expectation of success; and

3. The prior art reference (or references when combined) must teach or suggest all the claim limitations. See MPEP 2143 "Basic Requirements of a Prima Facie Case of Obviousness" (pages 2100-129: revised 2 May 2004).

However regarding criteria. 1. above (e.g. "suggestion or motivation" to combine) "If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the

references are not sufficient to render the claims prima facie obvious." See MPEP 2143.02 page 2100-132 citing *In re Ratti*, 270 F. 2d 810, 123 USPQ 349 (CCPA 1959). *In re Ratti was directed to a claim drawn to* "an oil seal comprising a bore engaging portion with outwardly biased **resilient** spring fingers inserted in a **resilient** sealing member". The court held that a secondary reference requiring a complete redesign of the primary reference oil seal from one which **required rigidity** to one which was **resilient** was not combinable (emphasis provided).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In the present case, the above rejection provides ample motivation to combine the references *inter alia* the substitution of one non-narcotic NSAID for another, especially where the secondary reference suggests benefits imparted by making the substitution as outlined in the rejection above.

Additionally, as pointed out in the above rejection, it is noted that the instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two

(or more) compositions each of which is taught by the prior art to be useful for the same purpose

The Examiner disagrees with applicant's position that one of ordinary skill in the art would narrowly construe the Baker reference to be limited to teaching the combination of a single NSAID (e.g. ibuprofen) with a single opioid (e.g. oxycodone) for treating pain. In this regard applicant fails to provide support for this assumption; nor can support be found in either the Baker or Penning references. In fact, both references point to a broad class of NSAID's which function to treat inflammatory pain which include the traditional NSAID's (e.g. aspirin) and the more recently improved NSAID's including ibuprofen and the newer COX-2 inhibitors.

Additionally, applicant's definition of the "principle of operation" of the Baker reference teaching is misguided. The "priniciple of operation" of the Baker reference is to combine NSAID's (e.g. ibuprofen) with opioids (e.g. oxycodone) in order to achieve improved pain relief as compared to the separate administration of the active agents. The unexpected benefit of achieving greater than additive pain relief (e.g. synergism) represents a strong teaching toward formulating additional compositions which include different (functionally equivalent) NSAID's, especially those with fewer side-effects as compared to traditional NSAID's as pointed out in the secondary reference.

Finally, substituting one functionally equivalent compound for another (e.g. non-opioid NSAID's ie. Cox inhibitors) to treat inflammatory pain is directly in line with sound scientific reasoning and established case law including *In re Kerkhoven* cited above.

The *In re Ratti* court's holding of non-combinable references where modifying primary reference *rigid parts of a device to obtain the claimed device which required resilient* parts; tantamount to a complete redesign, is simply not on point.

Accordingly, the above obviousness rejections are hereby maintained.

Relevant Prior Art of Record:

1 and 2. Engelhardt et al. Inflamm. Res. Vol. 44: pages 423-33 (1995) and Engelhardt, Brit. J. of Rheum. Vol. 35 (suppl.1) (1996) pages 4-12 teach the beneficial effects of new COX-2 NSAID's (e.g. meloxicam) as compared to the already established aspirin-like NSAID's .

3. Richardson et al. Drug Safety Vol. 15(4)(Oct. 1996) pages 249-260 teach the benefits of selective COX-2 inhibitors, including IBUPROFEN and MELOXICAM and 6-MNA as compared to traditional non-steroidal anti-inflammatory drugs (e.g. NSAID's such as aspirin). See e.g. abstract; pages 253-255

Note:. the Oshlack patent references cited in the new obviousness rejection above were raised in response to the new claims (particularly new claims 49) presented in the 10/29/04 amendment addressing sustained release formulations.

Conclusion

2. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Future Correspondences:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bennett Celsa
Primary Examiner
Art Unit 1639

BC
January 6, 2005